

## **REMARKS**

Claim 98 is amended in the present amendment, and claims 99-102 stand as originally entered in the Amendment filed on May 12, 2003. Support for the amendment to claim 98 may be found, for example, at page 3, lines 12-15; Example 10, pages 55 -56, especially page 56, lines 3-22; Example 12, pages 57-58, Figure 12, and elsewhere in the specification and claims as originally filed.

Claims 98-102 stand rejected under 35 U.S.C. §101 as allegedly not supported by a specific and/or substantial asserted utility or a well established utility. Claims 98-102 also stand rejected under 35 U.S.C. §112, first paragraph, the claims allegedly not being supported by a specific and/or substantial asserted utility or a well established utility so that one skilled in the art would not know how to use the claimed invention.

Applicants respectfully traverse these rejections.

### **I. The Rejections under 35 U.S.C. § 101**

Claims 98-102 stand rejected under 35 U.S.C. §101 as allegedly not supported by a specific and/or substantial asserted utility or a well established utility. However, as discussed in previous responses, several specific and substantial utilities are asserted in the specification as filed.

Moreover, claim 98, as amended, requires that the claimed polynucleotide, when fused with the transmembrane domain and intracellular domain of the Rse tyrosine kinase receptor, be effective to activate phosphorylation by the Rse tyrosine kinase receptor upon ligand-induced dimerization. Such activation may be useful in cellular based assays, as disclosed in the specification (see, *e.g.*, page 56, lines 3-22). Such utility is in addition to other utilities of polypeptides of SEQ ID NO: 17 and nucleic acid molecules

encoding them. Thus, the claim language itself recites a use for the claimed subject matter.

### Asserted Utilities

The Utility Examination Guidelines (66 Fed. Reg. 1092 (2001)) state that an invention complies with the utility requirement of 35 U.S.C. §101, if it has at least one asserted “specific, substantial, and credible asserted utility” or a “well-established utility.”

The specification as filed asserts and/or demonstrates utility including, for example, cell activation, treatment of disorders of the peripheral nervous system using ligands to GFR $\alpha$ 3, ligand screening, and other uses (see, *e.g.*, pages 18, 28-29, and 55-57 as discussed below). The GFR $\alpha$ 3 receptor was described in the application as being useful for antibody formation, treatment of disorders of the peripheral nervous system (using ligands to GFR $\alpha$ 3, such as antibody ligands), cell activation, production of chimeric receptors, ligand screening, and other uses. The novel receptors are useful for combining with a tyrosine kinase to effect phosphorylation, for example. Moreover, as has been discussed in previous papers, it was known in the art, and demonstrated in the specification as filed, that knowledge of a *native* ligand is not a pre-requisite for utility of a receptor.

Specific and substantial uses for the claimed nucleic acids, vectors, cells and processes include, for example, treatment of diseases or conditions of the peripheral nervous system such as "peripheral neuropathies associated with diabetes, HIV, chemotherapeutic agent treatments" and neuropathic pain (for example, at pages 28, lines 34-38; page 29, lines 1-14; and page 30, lines 11-14) and the stimulation of proliferation, growth, survival, differentiation, metabolism, or regeneration of GFR $\alpha$ 3- and Ret-containing cells (see, *e.g.*, page 18, lines 28-29). Applicants teach the use of nucleic

acids encoding GFR $\alpha$ 3 (or their complement) as, for example, hybridization probes in chromosome and gene mapping, tissue distribution studies, and in the generation of anti-sense RNA and DNA (see, *e.g.*, pages 27-29). Applicants in fact demonstrated how to measure binding of ligands to (chimeric) GFR $\alpha$ 3 receptors (page 56, lines 3-22). The specification further teaches antibodies to GFR $\alpha$ 3. The inventors disclose that ligands (such as antibodies) may be screened for agonist activity against these receptors (page 56, lines 19-22).

Such asserted utilities are credible for at least the reason that they "are consistent with the data of Example 5 in which a strong expression of GFR $\alpha$ 3 within the developing and adult sensory ganglia was observed" (specification, page 29, lines 1-2). Further uses, consistent with the expression data disclosed in the specification, include treatment of conditions of the autonomic nervous system and of the sympathetic nervous system, as discussed on page 29, lines 3-8.

The specification also teaches that the novel GFR $\alpha$ 3 molecules can dimerize, and that such dimerization can activate a kinase domain, and so be used to measure ligand-induced  $\alpha$ -subunit receptor activation (page 4, lines 24-27; page 55, line 10-page 56, line 22). The specification teaches how to provide GFR $\alpha$ 3 ligands (see, *e.g.*, page 56, lines 23-38 to page 57, lines 1-13). Measurements for ligand-mediated activation of (chimeric) GFR $\alpha$ 3 receptors are disclosed (see, *e.g.*, page 55, lines 31-37 to page 56, lines 1-22; page 57, lines 15-38 to page 58, lines 1-32). The specification teaches that receptor proteins may dimerize with a signaling component to link ligand binding with biological activation in a cell or cell membrane (see, *e.g.*, page 55, lines 11-17). Such dimerization may be used, *e.g.*, in "an assay to identify agonist antibodies and a natural ligand (or other agonists) for mammalian GFR $\alpha$ 3 follows the method described above for GFR $\alpha$ 2-Rse" (page 56, lines 5-6). Ligands to GFR $\alpha$ 3 are explicitly said to be useful for treatment

of diseases or conditions of the peripheral nervous system (see, *e.g.*, pages 28, lines 34-38 and 29, lines 1-14).

Thus, specific biological activity for the GFR $\alpha$ 3 receptor is taught in the application as filed. These activities and uses were taught in the provisional applications from which the non-provisional application claims priority. For example, U.S. Provisional Patent Application Serial Nos. 60/079,124 and 60/081,569 discuss tissue distribution of GFR $\alpha$ 3 (page 43, lines 12-27 and page 44, line 1 to page 45, line 9); antibodies to GFR $\alpha$ 3 on pages 30-37; the use of GFR $\alpha$ 3 antibodies on page 37, lines 2 to 29 and page 57, lines 1-27; chimeric receptors including GFR $\alpha$ 3 and their activation (page 52, line 8 to page 52, line 26); vectors (page 45, lines 14-23 and page 46, lines 14-18) and host cells (page 20, lines 2-11) comprising GFR $\alpha$ 3 message; and the treatment of diseases or conditions of the peripheral nervous system on page 4, lines 14-16 and on page 30, lines 1-24.

Applicants also disclose that the present invention provides an advantage derived from the "surprising, relative lack of expression of GFR $\alpha$ 3 in many organs, including notably brain, gut and kidney indicates that the ligand (and other agonists and antagonists) which binds this receptor lacks some side effects which may be associated with ligands which bind to GFR $\alpha$ 1 and GFR $\alpha$ 2 (GDNF and neurturin)" (page 29, lines 9-11). In addition, the inventors disclose that the novel receptors may be used in screening ligands (such as antibodies) for activity (which may be agonist activity or antagonist activity; see, *e.g.*, page 56, lines 19-22).

*The Novel GFR $\alpha$ 3 Receptor Discovered by the Inventors has Inherent Utility*

The claimed invention has inherent utility, which is now recognized in the art, and for this reason as well satisfies 35 U.S.C. §101.

The GFR $\alpha$ 3 receptor discovered and disclosed by Applicants, by its nature, is effective to bind ligands (whether natural or otherwise) and to affect cells in which it is expressed. It is well-known in the art that a ligand receptor binds ligands, and may be activated by such ligand-binding to induce an effect in the cell or cell membrane in which it is found (see, *e.g.*, page 2, lines 18-33 of that application). For example, it was known at the time the application was filed, and was disclosed in the application, that receptor proteins may dimerize with a signaling component to link ligand binding with biological activation in a cell or cell membrane (see, *e.g.*, page 55, lines 11-17). The GFR $\alpha$ 3 receptor was described in the application as being useful for antibody formation, treatment of disorders of the peripheral nervous system, cell activation, production of chimeric receptors, ligand screening, and other uses as discussed above.

Since such actions are inherent in the receptor itself, then such uses are inherent in the receptor itself. Receptor activation or inhibition upon ligand binding was well known in the art at the time of filing the application. These actions are disclosed in the application, are inherent in the GFR $\alpha$ 3 receptor, and are specific to that receptor; thus, for this reason and in this way as well, the specification therefore discloses specific utility for the receptor. These actions being inherent in the receptor, disclosure of the GFR $\alpha$ 3 receptor was effective to provide these asserted utilities to the public. Since the effects of ligand binding on receptors was well known, such asserted utility would be credible. Such uses are substantial, providing such “real world” uses as treatments of diseases or conditions of the peripheral nervous system. Accordingly, taken from the perspective of one of ordinary skill in the art, Applicants’ disclosure provides a reasonable use that is specific, substantial and credible.

#### *The Examiner's Burden*

An applicant’s assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101, “unless there is a reason for

one skilled in the art to question the objective truth of the statement of utility or its scope.” *In re Langer*, 503 F.2d 1380,1391, 183 USPQ 288, 297 (CCPA 1974); *see, also In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

However, the Examiner has not provided specific reasons or direct argument refuting these asserted utilities, and has failed to advance any evidence or solid scientific arguments why the uses disclosed by Applicants would not have been considered reasonable as of the priority date of this application, or would not provide any public benefit regarding these asserted utilities, and so has failed to rebut these assertions of utility.

Characterizing GFR $\alpha$ 3 as an orphan receptor, the Examiner suggests that since "GFR $\alpha$ 3 is thus an orphan receptor', the claimed polynucleotides have no specific nor substantial utility because further experimentation is necessary at the time of filing the instant invention to attribute a function and 'real world' utility to the claimed nucleic acid molecules" (Office Action dated July 24, 2002, page 4, lines 14-17). However, characterization of a receptor in such a way provides no indication of its utility or lack thereof. In fact, the pharmaceutical sciences and medicine provide many examples of useful drugs and therapeutics which act on receptors with unknown or uncharacterized native ligands, or whose native ligands were unknown at the time that useful functions for, or artificial ligands to, the receptor were identified.

Many "orphan receptors" are known to have utility. For example, the orphan receptor erbB2 (also known as c-erb2 and HER2) does not have a known *native* ligand and so is an orphan receptor: "ErbB2/Her2 is an orphan receptor that does not bind ligand alone but heterodimerizes with the other ErbB receptors for NRG [neuregulin] signaling." (Negro et al., "Essential roles of Her2/erbB2 in cardiac development and

function," Recent Prog Horm Res. 59:1-12 (2004), page 1, lines 7-8.) Yet, despite its being an "orphan receptor," ErbB2 is used to aid in the diagnosis of breast cancer and in the determination of a proper therapy for that disease. Moreover, the breakthrough drug HERCEPTIN® (trastuzumab), found to be effective in treating many women suffering from breast cancer, is an artificial ligand to the ErbB2 orphan receptor.

ErbB2 is not an isolated example of an "orphan receptor" that is useful. Activation of growth hormone secretagogues (synthetic molecules that affect release of growth hormone) by synthetic ligands can increase appetite and reverse age-related decline in growth-hormone secretion in aged patients (Smith et al., "Growth hormone secretagogues: prospects and potential pitfalls," *Best Pract Res Clin Endocrinol Metab.* 18(3):333-347 (2004)). Thus, "orphan receptors" having no known native ligand have proven to be clinically important and useful.

Such specific uses, proven in the clinic as well as the research laboratory, are clearly credible and substantial. Accordingly, mere characterization of a receptor as an "orphan receptor" cannot support an allegation of lack of utility under 35 U.S.C. §101.

Summary Regarding the Rejections Under 35 U.S.C. § 101

Thus, the Applicants have disclosed a novel receptor; have demonstrated methods for measuring activation of chimeric receptor constructs of the novel receptor; and have disclosed uses for the claimed subject matter. Applicants submit that the utility disclosed in the application, alone and when taken in view of subsequent publications, demonstrates a specific and/or substantial asserted utility or a well established utility as required by 35 U.S.C. §101.

Accordingly, for at least these reasons, Applicants respectfully submit that the rejections of Claims 98-102 under 35 U.S.C. §101 as allegedly lacking a specific and/or substantial asserted utility or well established utility is in error, and should be withdrawn.

## **II. The Rejections under 35 U.S.C. §112, first paragraph**

Claims 98-102 stand rejected under 35 U.S.C. §112, first paragraph, the claims allegedly not being supported by a specific and/or substantial asserted utility or a well established utility so that one skilled in the art would not know how to use the claimed invention.

Applicants note that the specification includes multiple examples of the utility of the subject matter of Claims 98-102, as discussed above. Thus, the application provides several examples of specific, substantial and credible utility for the present invention and of its use, and thereby teaches how to use the invention. Examples demonstrate such use (*e.g.*, page 55, line 31 to page 56, line 1-22, and page 57, line 15 to page 58 line 32, as discussed above). A person of skill in the art at the time the present invention was made, in view of the teachings of the specification, the general knowledge in the art at the time, and in view of the inherent uses and properties of the claimed nucleic acids, cells and processes would have known how to make and use the invention.

Moreover, amended claim 98 recites a particular capability of the polypeptides encoded by the claimed nucleic acid molecules, in that the claimed polynucleotide, when fused with the transmembrane domain and intracellular domain of the Rse tyrosine kinase receptor, is effective to activate phosphorylation by a domain of the Rse tyrosine kinase receptor upon ligand-induced dimerization. As discussed above, in addition to other utilities of polypeptides of SEQ ID NO: 17 and nucleic acid molecules encoding them, such activation may be useful in cellular based assays, and is explicitly taught by the specification and claims. Thus, one of ordinary skill in the art would know how to practice the claimed invention.

Accordingly, for reasons set forth above, the rejections of Claims 98-102 under 35 U.S.C. §112, first paragraph are believed to be overcome.



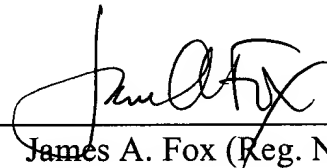
## CONCLUSION

In conclusion, Applicants respectfully submit that, for the above reasons, all outstanding rejections are overcome. As all of the claims in the present application are in condition for allowance, Applicants respectfully request the Examiner to bring all pending claims to issuance.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641, referencing Attorney's Docket No. 39766-0065 A.

Respectfully submitted,

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